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Cardiorespiratory Status After Treatment for Acute Lymphoblastic Leukemia

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The use of certain chemotherapeutic agents is associated with dose-related cardiotoxicity and, potentially, with restrictive lung disease. Therefore, we assessed the cardiopulmonary status and exercise capacity of 19 patients (pts; 9M:10F) 1.1 to 7.1 years (mean 4.6 ± 1.5 years) after successful treatment of acute lymphoblastic leukemia (ALL) with Dana Farber Cancer Institute protocols. As body mass and nutritional status may influence exercise capacity, we also evaluated their anthropometric status and the plasma levels of rapid turnover proteins. Seven pts designated as "standard risk for relapse" (SR) had received low cumulative doses of doxorubicin (50 ± 21 mg/m^2), while twelve pts at "high or very high risk for relapse" (HR/VHR) had received higher doses (349 ± 16 mg/m^2). The evaluations included a questionnaire, anthropometric assessments, echocardiography, pulmonary function studies, exercise testing, and nutritional assays. Patients' data were compared with published normative data or with control values from our laboratories. In addition, we compared SR pt data with HR/VHR pt data.

No pt had overt symptoms or signs of cardiorespiratory compromise. The pts had a higher percent of body fat than age-matched healthy controls (29.7 ± 7.9% vs. 20 ± 6%; $P < 0.001$). On echocardiography, cardiac systolic function was within normal limits in all. However, HR/VHR pts had lower left ventricular (LV) shortening fractions than SR pts ($P < 0.05$). LV filling velocity, indicative of diastolic function (the E/A ratio), was normal in most pts. Pulmonary function studies were normal. Exercise capacity was below predicted in most cases but heart rates at peak exercise and leg muscle function were within normal limits, suggesting a deconditioned state. Plasma levels of rapid turnover proteins were also normal.

Despite lack of overt morbidity in our pt population, subtle abnormalities persist in cardiac function while pulmonary function is normal. Longitudinal studies will identify if further abnormalities or overt morbidity develop. In later years, continuing obesity and a sedentary state may contribute to clinically relevant heart disease.

Key words: acute lymphoblastic leukemia, cardiorespiratory status, exercise, nutritional status

INTRODUCTION

Intensive multiagent chemotherapy has revolutionized the treatment of childhood leukemias with progressive gains in survival rates [1]. However, use of the anthracyclines, such as doxorubicin, is associated with dose-related cardiotoxicity [2,3], while other antileukemic agents may cause restrictive lung disease [4]. As the first stage in a longitudinal study of outcomes in survivors of acute lymphoblastic leukemia treated on the Dana Farber Cancer Institute protocols, we evaluated cardiopulmonary status at rest and on exertion in 19 patients at least a year after conclusion of successful therapy. Because body mass and nutritional status may influence the function of muscles involved in exercise, such as the thoracic wall and leg muscles, we evaluated anthropometric status and the plasma levels of rapid turnover proteins, retinol-binding protein, transthyretin and the amino acid 3-methylhistidine. Both retinol-binding protein and transthyretin have small body pools with half-lives of approximately 12 hours and 2 days, respectively [5] and therefore they are affected by acute changes in nutrition. 3-Methylhistidine is an amino acid derived from the breakdown of skeletal muscle proteins. Measurements of these proteins would therefore indicate the protein-energy nutritional status at the time of exercise testing. In addition, to assess the cumulative effect of doxorubicin on the heart, we

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compared the results obtained in those children who had received a low cumulative dose of doxorubicin with the results in those who had received high cumulative doses of this drug.

MATERIALS AND METHODS

Patient Population

Subjects were recruited from the Hematology-Oncology Service in the Children's Hospital at Chedoke McMaster. Using a protocol approved by the McMaster University Research Project Advisory Committee for Clinical Studies, informed consent was obtained from parents of all patients prior to inclusion in the study. We enroled 19 patients treated between January 1984 and April 1990 for childhood acute lymphoblastic leukemia (ALL) with several Dana Farber Cancer Institute (DFCI) protocols. Only patients who had been in continuous remission for more than a year after completing treatment and who were tall enough to undertake the exercise studies using a cycle ergometer were included in the study. At the time of diagnosis, seven had been designated as "standard risk for relapse" by DFCI criteria [1] and had received low cumulative doses of doxorubicin. Twelve had been considered "high and very high risk for relapse" by DFCI criteria and had received higher cumulative doses of doxorubicin. The evaluation of all patients included a questionnaire, anthropometric assessment, echocardiography, pulmonary function studies, exercise testing, and plasma protein analysis. Either published normative data or control values currently in use in our cardiopulmonary function and nutrition laboratories were used for comparison with the information obtained in the patient investigations.

Questionnaire

A questionnaire was designed to identify symptoms suggestive of cardiovascular compromise on exertion, and factors which might influence the results of this study, such as smoking or asthma. The questionnaire was used also to establish a New York Heart Association (NYHA) classification [6] for each patient. The medical charts were reviewed for previous episodes of lower respiratory tract infection.

Anthropometric Assessments

Height and weight were measured by standard procedures and compared with the standards of Tanner and Whitehouse [7]. Patients underwent a physical examination by one of the pediatric hemato-oncologists, during which the Tanner pubertal stage was recorded. The percentage of body fat was calculated from triceps and subscapular skinfold thickness (average of three measurements) taken from the nondominant side using a Harpenden calliper [8]. Lean body mass was calculated from the product of weight and 1 minus percentage of body fat.

Echocardiography

The evaluation consisted of M-mode, two-dimensional echocardiography and Doppler assessment of left ventricular systolic and diastolic function. For all parameters, a mean of three observations from three different time points during the study was used in the calculations.

Systolic function. M-mode echocardiograms, directed by two-dimensional echocardiography with simultaneous ECG tracing, were recorded in the parasternal long and short axis views according to standards recommended by the American Society of Echocardiography [9]. Parameters included fractional shortening and left ventricular end diastolic internal diameter [9]. End-systolic wall stress, an indicator of left ventricular (LV) afterload, was determined from M-mode measurements at end-systole and simultaneous cuff systolic blood pressures (Dinamap™, Critikon Inc., Florida) [10].

Diastolic function. In the apical four-chamber view, the Doppler sample volume was placed near the tips of the mitral valve leaflets, distal to the annulus of the valve. Transmitral flow velocity patterns were recorded, and peak velocities during rapid filling (peak E velocity) and during atrial contraction (peak A velocity) were calculated. Values for the E/A ratio were also calculated and compared to published normative values [11].

Pulmonary Function Tests

The patients performed expiratory spirometry using a rolling-seal spirometer as per the American Thoracic Society standards (S and M Instrument Co. Pulmo-Screen II, Doyles Town, Pennsylvania) [12,13]. Lung volumes were measured by whole-body plethysmography (Med Graphics, Minneapolis, MN) [14]. Diffusing capacity (DL_{co}) was determined by single breath carbon monoxide diffusing capacity [14,15]. All results were expressed as percentages of predicted values. Respiratory muscle strength was determined from static maximal mouth pressures measured at functional residual capacity, and expressed in cm H_2O.

Exercise Testing

The patients performed a progressive exercise test with increments of 100 kpm/min (16.3 w) every minute to symptom-limited exhaustion using an electronically braked cycle ergometer. Results were expressed in absolute terms, and as percentages of predicted values. The equations used were gender appropriate, based on height and workload achieved [16].

Leg muscle function was analyzed during a 30-sec maximal effort made on an isokinetic cycle ergometer [17]. During isokinetic cycling at a preset speed, deformational force on the pedal shafts is recorded as torque. Work for each pedal stroke is equal to the average torque multiplied by both the rotational velocity and the time for the pedal stroke. Work for the 30 sec, the sum of the work for each pedal stroke, is reported in kJ units corrected for kilogram lean body mass (J/kg) [17].

Nutritional Assays

Hemoglobin and hematocrit were measured from a capillary blood sample by standard Coulter counter methods. A venous blood sample was obtained from 14 subjects and the plasma was immediately separated and stored at −70°C prior to analysis for retinol-binding protein, prealbumin (transthyretin) and 3-methylhistidine. Patients had eaten breakfast 3–4 hours prior to sampling. Retinol-binding protein and transthyretin were measured by enzyme-linked immunosorbent assays [18]. The 3-methylhistidine was measured by high performance liquid chromatography [19]. Values of 3-methylhistidine in blood indicate skeletal muscle stores and are not influenced by diet or 3-methylhistidine derived from other tissues as 24-hour urine values may be [19]. Results are compared with in-house values from 14 healthy control subjects, M/F = 9/5, ages 13.2 ± 3.1 years, who were 101 ± 14% of ideal body weight.

Statistical Analysis

Echocardiographic and pulmonary function data which were more than 2 S.D. below or above normal were considered abnormal. The anthropometric, exercise, leg muscle function and plasma protein data were compared to in-house control data using the Student's two-sided unpaired t-test. Comparisons between the "standard risk for relapse" (SR) and "high or very high risk for relapse" (HR/VHR) groups were also made using an unpaired t-test. Chi-squared analyses were used to compare the NYHA classification data from the SR and HR/VHR groups. Linear regression analysis was performed on the resting pulmonary function tests, age at diagnosis and time off therapy, as well as on 30-sec leg work and lean body mass. Data are expressed as the mean ± S.D. unless stated otherwise. P values of <0.05 were considered statistically significant.

RESULTS

Patient Population (Table I)

Of 20 eligible patients, one was excluded because of noncompliance. The remaining 19 patients consisted of 9 males, 10 females, mean age 13.0 ± 3.5 years (range 7.7 − 23.8 years, median 12.3 years). Their mean age at diagnosis was 6.1 ± 4.3 years, (range 1.5–17.7 years, median 4.6 years), mean time off therapy 4.6 ± 1.5 years (range 1.1–7.1 years, median 4.4 years). Seven SR patients had received low cumulative doses of doxorubicin (mean 50 ± 21 mg/m^2) and 12 HR and VHR patients had received higher cumulative doses of doxorubicin (mean 349 ± 16 mg/m^2; $P < 0.01$ SR vs. HR/VHR). None of the patients received mediastinal irradiation. Surgical removal of a right atrial thrombus, associated with catheter placement, was required in one patient in the HR category, after 10 months on therapy and 3 years prior to study. One patient had an episode of bacterial pneumonia (Hemophilus influenzae) and four patients had Pneumocystis carinii pneumonia during therapy. All patients were free of symptomatic illness at the time of testing.

TABLE I. Demographic Data and Results of Questionnaire in Survivors of DFCI Protocols†

	SR[a] (n = 7)	HR/VHR[b] (n = 12)
Protocol		
84.01 HR	—	2
85.01 SR	7	—
85.01 HR	—	9
87.01 HR	—	1
Age at diagnosis (years)	4.5 ± 1.5	7.1 ± 5.1
Age at study (years)	11.5 ± 0.9	13.9 ± 4.2
Number of years off therapy	4.6 ± 0.8	4.6 ± 1.8
Doxorubicin dose mg/m^2	50 ± 21	349 ± 16*
NYHA[c] class I	n = 6	n = 5
NYHA class II	n = 1	n = 7

†Values are expressed as mean (± 1 S.D.).
*$P < 0.01$ SR vs. HR/VHR.
[a]SR, Standard risk for relapse.
[b]HR/VHR, High or very high risk for relapse.
[c]NYHA, New York Heart Association.

Questionnaire

Eleven patients were in NYHA class I, eight patients were in NYHA class II ($P = 0.14$ SR vs. HR/VHR). The most frequent complaints were fatigue and shortness of breath on exertion. There were no episodes of chest pain on exertion, and none of syncope or palpitations. Three patients had asthmatic episodes treated by physicians; in one patient the attacks preceded the diagnosis of ALL. None of the patients smoked.

Anthropometric Assessments

Anthropometric assessments were available in 14 patients (5 SR, 9 HR/VHR). The patients had a percent ideal weight of 113.6 ± 22.5 (mean ± S.D.) and percent body fat of 29.7 ± 7.9 which was high relative to the value of 20 ± 6% observed in 14 healthy control subjects of similar ages weighing 101 ± 14% of ideal body weight ($P < 0.001$). The body mass index of the ALL

patients was 22.1 ± 4.6 (range 15.5–29.8) and of the controls was 19.9 ± 3.1 (range 15.2–25.8) (P = not significant). There were no differences in the anthropometric parameters of the SR and HR/VHR groups.

Echocardiography

Echocardiograms obtained in 18 patients showed normal regional wall motion and no structural anomalies.

Systolic function. Parameters of systolic function were within the normal range in all patients studied. However, shortening fraction was significantly lower in the HR/VHR group (32.6 ± 0.75%) than in the SR group (39.0 ± 1.27%, $P < 0.05$). Left ventricular end-systolic wall stress was within accepted limits in all those studied: SR-mean 50.5 ± 9.2 g/cm^2, range 40.9–57.9 g/cm^2 and HR/VHR-mean 53.7 ± 12.6 g/cm^2, range 41.1–79.0 g/cm^2.

Left ventricular end diastolic internal diameter (LVED) corrected for body surface area (BSA) was normal in 17 patients. One SR patient had an LVED just above the 95th centile for BSA.

Diastolic function. Peak E (filling) velocities were normal in all patients, while peak A (atrial) velocities were decreased in five patients (2 SR, 3 HR). E/A ratios were in the normal range (1.3–2.1) except in these five pts where they ranged from 2.5 to 3.5. There was no statistically significant difference between the E/A ratios in the SR and HR/VHR patients.

Pulmonary Function Tests

All pulmonary function measures were within normal limits: FEV_1 92.8 ± 11.8% predicted, FVC 92.6 ± 10.3% predicted, FEV_1/FVC ratio 85.4 ± 6.4%, TLC 98.6 ± 13.6% predicted, RV/TLC ratio 22.6 ± 7.4%. DL_{co} 105.4 ± 23.3% predicted (16/17 studied), maximum inspiratory pressure 76.8 ± 17.4 cm H_2O; maximum expiratory pressure 86.6 ± 17.9 cm H_2O. Two males, aged 12 and 17 (HR) had FEV_1s of 73% and 74%, respectively (minimally decreased); none of the subjects had FVCs outside the normal range. There was no correlation between age at diagnosis or time off therapy and any lung function parameter. There was no difference in any pulmonary function parameters between SR and HR/VHR groups.

Exercise Testing

Twelve patients (5 SR, 7 HR/VHR) completed the progressive exercise test. The maximal capacity attained was 93.0 ± 31.9 watts, representing 67.5 ± 24.8% predicted [16].

To evaluate the heart rate response to exercise, the maximal heart rate attained at the cessation of exercise was compared to predicted values [16]. In the study patients, the maximal heart rate on exercise was 97.4 ± 12.3% predicted. There was no difference in heart rate responses to maximal exercise in the HR/VHR (96.5 ± 15.1% predicted) versus SR group (98.7 ± 8.2% predicted).

Due to noncompliance, leg muscle function studies were available in only 11 study patents (5 SR, 6 HR/VHR). For these 11 patients, 30-sec leg work correlated with lean body mass ($r = 0.691$, $P < 0.02$, intercept not different from 0). There was no difference between SR and HR/VHR groups with respect to absolute leg work (SR: 7909.7 ± 977.2; HR/VHR: 9832.1 ± 2214.3 J) or leg work relative to lean body mass (SR: 244.7 ± 14.5; HR/VHR: 251.2 ± 46.7 J/kg).

Nutritional Assays

Plasma retinol-binding protein was lower in patients compared with healthy control subjects (24.4 ± 4.2 vs. 29.8 ± 7.3 mg/L, respectively, $P < 0.05$). However, patients and control subjects had similar values for plasma transthyretin (150.8 ± 37.5 vs. 179.3 ± 59.6 mg/L) and 3-methylhistidine (9.3 ± 2.0 vs. 10.9 ± 4.2 μmol/L). None of the values correlated with body weight as a percentage of ideal. Values did not differ between risk groups.

DISCUSSION

This study involves 19 patients with ALL who were survivors (>4 years) of DFCI protocols, without overt symptoms or signs of cardiorespiratory compromise. We identified that the patients were at risk of obesity with mean percentage body fat of 29.7 ± 7.9%. On echocardiography, although cardiac systolic and diastolic functions were within the normal range, prior use of higher doses of doxorubicin was associated with a lower shortening fraction ($P < 0.05$). LV end-systolic wall stress was within accepted limits. Pulmonary function, maximal heart rate response to exercise, leg muscle function and nutritional status were within normal limits and did not differ between the SR and HR/VHR groups. Exercise tolerance was below predicted values.

Anthracycline use is well-recognized as a major cause of cardiotoxicity in patients with ALL [1–3]. The myocardial dysfunction, which may be fatal, can occur at any time during therapy or years after cessation of therapy [1–3,20]. While the use of more than 550 mg/m^2 of doxorubicin has been associated with overt cardiotoxicity, it is not clear whether there is a safe cumulative dose or a safe age for treatment of ALL with this chemotherapeutic agent. Diagnosis of early cardiac damage has, therefore, become a priority in all patients.

Biancaniello et al. [21], in a prospective echocardiographic study of 46 children, found that the left ventricular shortening fraction was more useful in detecting cardiotoxic effects than the systolic time intervals. A study by Lipschultz et al. [3] on 115 survivors of childhood

leukemia demonstrated echocardiographically detectable abnormalities of LV contractility and/or afterload in 57%. The factors which influenced cardiotoxicity (cumulative dose, age at treatment and length of follow-up) were interrelated. However, multivariate analyses demonstrated that the cumulative dose was the most significant predictive factor for both decreased contractility and increased afterload. Patients were usually asymptomatic and symptoms correlated poorly with echocardiographic indices or with the duration of exercise.

The echocardiographic findings in our patients are in keeping with Lipschultz's observations [3]. LV end-diastolic dimensions were within normal limits in all but one SR patient. Left ventricular contractility was normal in all those studies, but there was a significant difference in LV shortening fraction between the SR and HR/VHR groups. We did not identify abnormalities in LV end-systolic wall stress which would have indicated increased LV afterload but this could have been influenced by the small numbers of patients studied. LV diastolic function, as determined by the E/A ratio, was normal in most instances. It is interesting that the rapid LV filling phase (E velocity) was normal in our patients while the velocity during atrial contraction was reduced in five patients. Results obtained from radionuclide angiograms by Lee et al. [11], in 12 adults who received doxorubicin for varying malignancies, differ in that both rapid and slow LV filling were reduced. There are several differences between Lee's group and ours. Although we can assume that LV diastolic function in our patients was normal before doxorubicin treatment, we have no information immediately after the final dose of doxorubicin. The finding of changes in the atrial contraction phase of LV filling in five of our patients may be relevant as an early indicator of abnormalities in diastolic function. The implications of these findings and the relevance to long-term morbidity are uncertain. Longitudinal studies will be necessary to identify the incidence of late myocardial dysfunction.

Mild restrictive lung disease has been reported as a potential sequel to treatment for ALL with UKALL protocols [4,22]. It has not been documented previously whether restrictive lung disease occurs following treatment with DFCI protocols. Our pulmonary function studies would suggest that all parameters of lung function are normal in such survivors. However, as our results represent a cross-sectional evaluation, longitudinal studies will be necessary to confirm that long-term pulmonary sequelae of the DFCI protocols do not occur.

It is unfortunate that we were unable to obtain complete results during exercise testing. The decreased work capacity was due to symptom limitation. It is likely that maximal exercise efforts may not have been achieved as the exercise tests were performed towards the end of a long study day. However, maximal heart rates at cessation of exercise were within normal limits. In the absence of abnormalities in pulmonary function or in other parameters, e.g., leg muscle function, this would suggest a deconditioned state due to lack of physical training. Evaluation of exercise capacity during exercise and noninvasive determinations of cardiac output would provide important information which would complement resting evaluations of both cardiac and pulmonary function [23]. These would constitute worthwhile investigations in survivors of ALL.

Leg muscle function correlated with lean body mass and was not different between the two risk stratification groups. Although we do not have normative data for this age group, we compared our results with a subgroup of previously reported [24] adolescents and young adults with cystic fibrosis (CF), whose lean body mass (39.6 ± 3 kg) was similar to those of our patients (35.9 ± 5.4 kg). In the CF patients, leg muscle function was at the lower limit of normal ($78.9 \pm 31.4\%$ predicted for age and height; $78.0 \pm 26.5\%$ predicted for age and weight) [25]. The leg muscle function data in our ALL patients (work/kg lean body mass = 248.6 ± 36.3 J/kg) were similar to data in the CF group (215.6 ± 75.7 J/kg). Although requiring confirmation by comparison with an age-matched healthy group, these results suggest that leg muscle function is appropriate for the amount of lean body mass in children who survived ALL after treatment with DFCI protocols.

The explanation for lower retinol-binding protein levels in the patients in this study, relative to healthy control subjects, is uncertain. Both patients and control subjects were free of known infection, liver disease or other nutritional deficiencies, such as of vitamin A or zinc, known to affect retinol-binding protein [5]. There was no evidence of catabolism, as suggested by the normal blood 3-methylhistidine. Although the levels were lower in patients, these fell within reported normal ranges [5]. Thus, it is unlikely that poor nutritional status would have interfered with exercise tolerance or muscle function.

CONCLUSIONS

Our results indicate that, despite successful treatment of childhood ALL and the lack of overt morbidity, subtle abnormalities may persist. The importance of the cumulative effect of doxorubicin on cardiac function is again highlighted. In the short term, pulmonary function is normal. However, obesity and the adoption of a sedentary lifestyle may contribute to morbid events in later years.

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